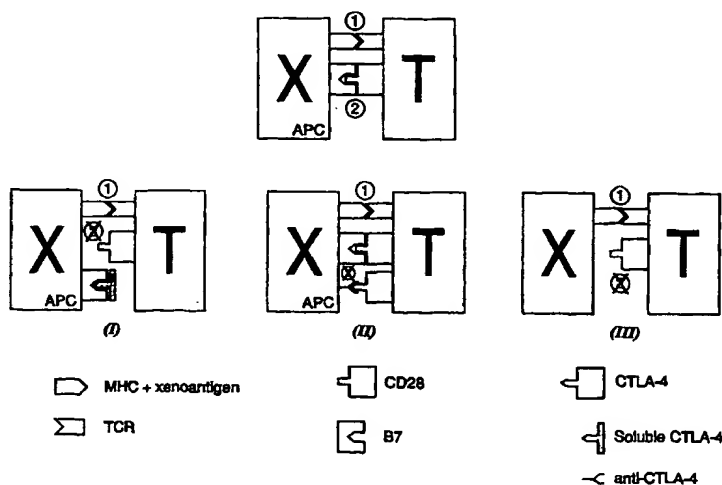




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<b>(21) International Application Number:</b> PCT/GB99/01350 <b>(22) International Filing Date:</b> 30 April 1999 (30.04.99)  <b>(30) Priority Data:</b> 9809280.2                      30 April 1998 (30.04.98)                      GB  <b>(71) Applicant (for all designated States except US):</b> IMPERIAL COLLEGE INNOVATIONS LIMITED [GB/GB]; 47 Prince's Gate, Exhibition Road, London SW7 2QA (GB).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> LECHLER, Ian, Robert [GB/GB]; Hammersmith Hospital, London W12 0NN (GB). DORLING, Anthony [GB/GB]; Hammersmith Hospital, London W12 0NN (GB).  <b>(74) Agent:</b> HOWARD, Paul, Nicholas; Carpmaels & Ransford, 43 Bloomsbury Square, London WC1A 2RA (GB).		<b>(81) Designated States:</b> AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>Without international search report and to be republished upon receipt of that report.</i>

**(54) Title:** IMMUNOSUPPRESSION BY BLOCKING T CELL CO-STIMULATION SIGNAL 2 (B7/CD28 INTERACTION)

**(57) Abstract**

The invention provides means and methods for inhibiting T-cell mediated rejection of a xenotransplanted organ by blocking the delivery of co-stimulatory signal 2 (the B7/CD28 interaction) in order to prevent the activation of xenoreactive T-cells in the recipient. In a first aspect, co-stimulation is prevented by administration to the organ recipient of a soluble form of CTLA-4 from the xenogeneic donor organism. This preferentially binds B7 on the xenograft and blocks the interaction between B7 on the xenogeneic donor cells and CD28 on recipient T-cells. In a second aspect, co-stimulation is antagonised by expressing a ligand for CTLA-4 on the xenogeneic donor cells. This ligand binds to CTLA-4 on activated T-cells of the recipient and antagonises signal 2. In a third aspect, co-stimulation is prevented by expressing recipient organism MHC class II on the surface of the cells of the xenogeneic donor organ. The donor cells are thus able to present xenoantigens to a recipient T-cell in the context of self-MHC class II. If the donor cells do not express B7, or if B7 is blocked, the xenoreactive recipient T-cell becomes anergic.

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